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(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) 2,9-Disubstituted Purin-6-Ones

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(57) 18 Claims

Notice: This application is as filed and may therefore contain an incomplete specification.

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2,9-Disubstituted purin-6-ones

Abstract

2,9-Disubstituted purin-6-ones are prepared by acylating correspondingly substituted aminoimidazoles in a first step and then cyclizing the product to the purine. The new 2,9-disubstituted purin-6-ones can be employed as active compounds in medicaments, in particular for the treatment of inflammations, thromboembolic and cardiovascular diseases and diseases of the urogenital system.

2,9-Disubstituted purin-6-ones

The present invention relates to 2,9-disubstituted purin-6-ones, a process for their preparation and their use in medicaments, in particular for the treatment of inflammations, thromboembolic and cardiovascular diseases and diseases of the urogenital system.

Some 2-phenyl-substituted 6H-purin-6-ones are known from the publications J. Pharm. Sci., 74 (10), 1082-85, 1985 and J. Hetero. Chem. 19 (1), 33-40, 1982.

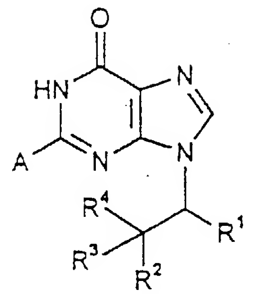
1H-9-Methyl-substituted purines and oxazolopyrimidines have furthermore been described [in this context cf. Khim.-Farm. Zh. 8(4), 26-8, 1974 and Bull. Chem. Soc. Jap. 43 (12), 3509-13 (1970)].

9-Substituted hypoxanthines are furthermore known from JP 47 021 434.

Moreover, purine derivatives having a regulating action on plant growth and 2-substituted 9-(4-methylbenzyl)-9H-purines having an anti-rhinovirus action are known [cf. Egypt. J. Chem., Vol. Data 1990, 33 (3), 243-53, 1991 and J. Med. Chem. 32 (1), 218-24, 1989].

Phosphodiesterases (PDEs) play an essential role in the regulation of the intracellular cGMP and cAMP level. Of the phosphodiesterase isoenzyme groups PDE I to PDE V described to date [nomenclature according to Beavo and Reifsnyder (cf. Beavo, J.A. and Reifsnyder, D.H.: Trends in Pharmacol. Sci 11, 150 - 155 (1990))], the Ca-calmodulin-activated PDE I, the cGMP-stimulatable PDE II and the cGMP-specific PDE V are essentially responsible for the metabolism of cGMP. Because of the different distribution of these cGMP-metabolizing PDEs in tissue, selective inhibitors should raise the cGMP level in the corresponding tissue depending on the tissue distribution of the corresponding isoenzyme. This can lead to a specific antiaggregatory, antispastic, vasodilating, antiarrhythmic and/or antiinflammatory action.

The present invention thus relates to 2,9-disubstituted purin-6-ones of the general formula (I)



(I),

in which

R^1 represents straight-chain or branched alkyl having 2 to 10 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by halogen, nitro, cyano or by straight-chain or branched alkyl having up to 6 carbon atoms,

R^2 represents hydrogen, hydroxyl or azido, or represents straight-chain or branched alkyl having up to 6 carbon atoms, or represents a group of the formula $-O-SO_2R^5$,

wherein

R^5 denotes straight-chain or branched alkyl having up to 4 carbon atoms or phenyl,

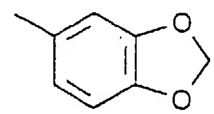
R^3 represents hydrogen,

or

R^2 and R^3 together form the radical of the formula =O,

R^4 represents hydrogen, or represents straight-chain or branched alkyl having up to 4 carbon atoms,

and

A represents a radical of the formula  or

represents straight-chain or branched alkyl having up to 20 carbon atoms, or represents cycloalkyl having 3 to 7 carbon atoms, or represents phenyl, which are optionally substituted up to 2 times in an identical or different manner by halogen, carboxyl, trifluoromethyl, nitro, cyano or by straight-chain or branched alkyl, alkoxycarbonyl or alkoxy having in each case up to 5 carbon atoms, which in their turn can be substituted by phenyl, and/or the rings are optionally substituted by phenyl, which in turn can be substituted by straight-chain or branched alkoxy having up to 5 carbon atoms,

and tautomers and salts thereof.

The substances according to the invention can also be in the form of salts. Physiologically acceptable salts are preferred in the context of the invention.

Physiologically acceptable salts can be salts of the compounds according to the invention with inorganic or organic acids. Preferred salts are those with inorganic acids, such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or salts with organic carboxylic or sulphonic acids, such as, for example, acetic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, lactic acid, benzoic acid or methanesulphonic acid, ethanesulphonic acid, phenylsulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid.

The compounds of the general formula (I) according to the invention can occur in various stereochemical forms which either behave as mirror images (enantiomers) or do not behave as mirror images (diastereomers). The invention relates both to the antipodes and to the racemic forms, as well as the diastereomer mixtures. The racemic

forms, like the diastereomers, can be separated into the stereoisomerically uniform constituents in a known manner.

Preferred compounds are those of the general formula (I)

in which

R^1 represents straight-chain or branched alkyl having 2 to 8 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by fluorine, chlorine, bromine, nitro, cyano or by straight-chain or branched alkyl having up to 4 carbon atoms,

R^2 represents hydrogen, hydroxyl or azido, or represents straight-chain or branched alkyl having up to 4 carbon atoms or a group of the formula $-O-SO_2R^5$,

wherein

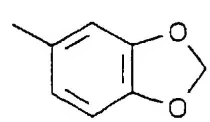
R^5 denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl,

R^3 represents hydrogen,

or

R^2 and R^3 together form the radical of the formula =O,

R^4 represents hydrogen, or represents straight-chain or branched alkyl having up to 3 carbon atoms, and

A represents a radical of the formula  or

represents straight-chain or branched alkyl having up to 19 carbon atoms, or represents cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl, or represents phenyl, which are optionally substituted up to 2 times in an identical or different manner by fluorine, chlorine, bromine, carboxyl, nitro, hydroxyl or by straight-chain or branched alkyl, alkoxycarbonyl or alkoxy having in each case up to 4 carbon atoms, which in their turn can be substituted by phenyl, and/or the rings are optionally substituted by phenyl, which in turn can be substituted by straight-chain or branched alkoxy having up to 4 carbon atoms,

and tautomers and salts thereof.

Particularly preferred compounds are those of the general formula (I)

in which

R^1 represents straight-chain or branched alkyl having 2 to 7 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by fluorine, chlorine, bromine, nitro, cyano or by straight-chain or branched alkyl having up to 3 carbon atoms,

R^2 represents hydrogen, hydroxyl or azido, or represents straight-chain or branched alkyl having up to 3 carbon atoms or a group of the formula $-OSO_2R^5$,

wherein

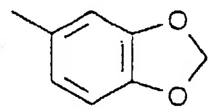
R^5 denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl,

R^3 represents hydrogen,

or

R^2 and R^3 together form the radical of the formula =O,

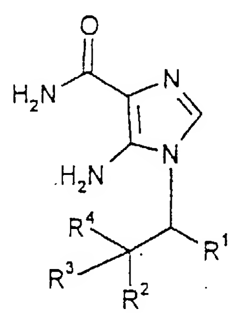
R^4 represents hydrogen, or represents straight-chain or branched alkyl having up to 3 carbon atoms, and

A represents a radical of the formula  or

represents straight-chain or branched alkyl having up to 18 carbon atoms, or represents cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl or phenyl, which are optionally substituted up to 2 times in an identical or different manner by fluorine, chlorine, bromine, carboxyl, nitro, hydroxyl or by straight-chain or branched alkyl, alkoxycarbonyl or alkoxy having in each case up to 3 carbon atoms, which in their turn can be substituted by phenyl, and/or the rings are optionally substituted by phenyl, which in turn can be substituted by straight-chain or branched alkoxy having up to 3 carbon atoms,

and tautomers and salts thereof.

A process has furthermore been found for the preparation of the compounds of the general formula (I) according to the invention, characterized in that compounds of the general formula (II)



(II)

in which

R^1, R^2, R^3 and R^4 have the abovementioned meanings,

are first converted, by reaction with compounds of the general formula (III)

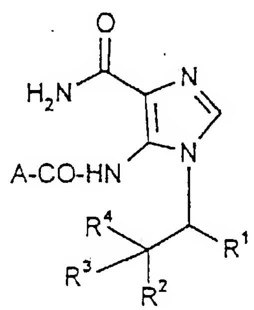
A-CO-Cl (III)

in which

A has the abovementioned meaning,

in inert solvents and in the presence of a base,

into the compounds of the general formula (IV)



(IV)

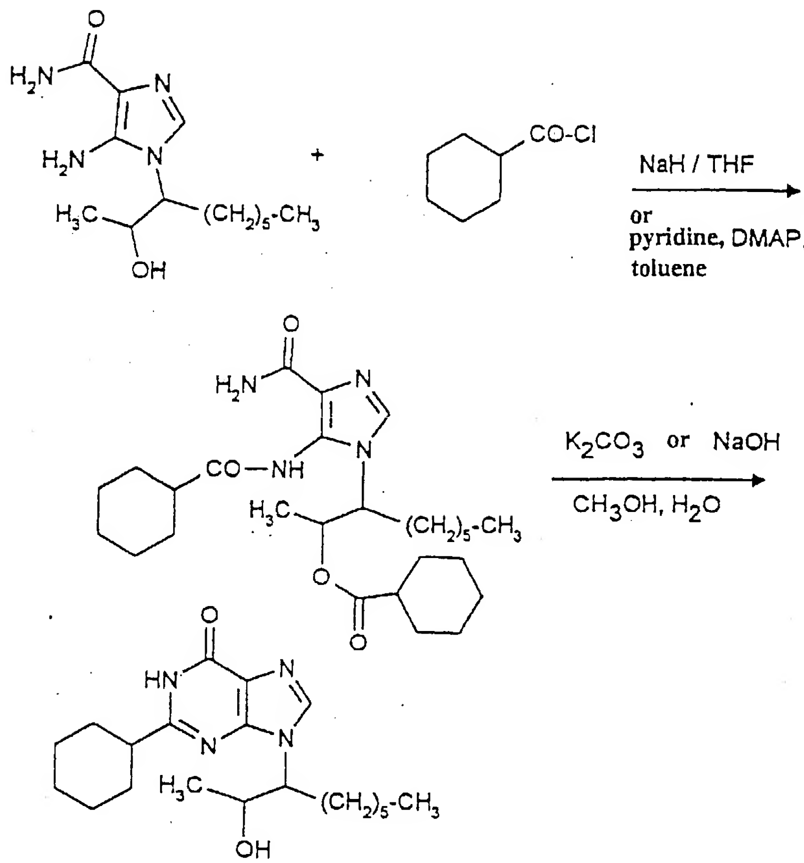
in which

A, R^1, R^2, R^3 and R^4 have the abovementioned meaning,

these are cyclized in a second step in inert solvents and in the presence of a base,

and the substituents R^1, R^2, R^3 and R^4 are introduced or derivatized by acylation, oxidation and/or azide exchange.

The process according to the invention can be illustrated by way of example by the following equation:



Inert organic solvents which do not change under the reaction conditions are suitable for the first step of the process. These include, preferably, ethers, such as, for example, diethyl ether, dioxane, tetrahydrofuran or glycol mono- or dimethyl ether, halogenated hydrocarbons, such as methylene chloride, chloroform or carbon tetrachloride, dichloroethylene or trichloroethylene, ethyl acetate, toluene, acetonitrile, hexamethylphosphoric acid triamide, pyridine and acetone. It is of course possible to employ mixtures of the solvents. Tetrahydrofuran, toluene or pyridine are particularly preferred.

Suitable bases are in general alkali metal hydrides or alcoholates, such as, for example, sodium hydride or potassium tert-butylate, or cyclic amines, such as, for example, piperidine, pyridine or dimethylaminopyridine, or C_1-C_4-alkylamines, such as, for example, triethylamine. Sodium hydride, pyridine or dimethylaminopyridine are

preferred.

The base is in general employed in an amount of 1 mol to 4 mol, preferably 1.2 mol to 3 mol, in each case per mole of the compounds of the general formula (II).

The reaction temperature can in general be varied within a relatively wide range. The reaction is in general carried out in a range from -20°C to 200°C, preferably from 0°C to 25°C.

In one variant, the reaction is carried out in pyridine, to which a catalytic amount of DMAP is added. If appropriate, toluene can also be added.

Suitable solvents for the cyclization are the customary organic solvents. These include, preferably, alcohols, such as methanol, ethanol, propanol, isopropanol or butanol, or ethers, such as tetrahydrofuran or dioxane, or dimethylformamide or dimethyl sulphoxide. Alcohols, such as methanol, ethanol, propanol or isopropanol, are particularly preferably used. It is also possible to employ mixtures of the solvents mentioned.

Suitable bases for the cyclization are the customary inorganic bases. These include, preferably, alkali metal hydroxides or alkaline earth metal hydroxides, such as, for example, sodium hydroxide, potassium hydroxide or barium hydroxide, or alkali metal carbonates, such as sodium carbonate or potassium carbonate or sodium bicarbonate, or alkali metal alcoholates, such as sodium methanolate, sodium ethanolate, potassium methanolate, potassium ethanolate or potassium tert-butanolate. Potassium carbonate and sodium hydroxide are particularly preferred.

In carrying out the cyclization, the base is in general employed in an amount of 2 to 6 mol, preferably 3 to 5 mol, per mole of the compounds of the formula (IV).

The cyclization is in general carried out in a temperature range from 0°C to 160°C, preferably at the boiling point of the particular solvent.

The cyclization is in general carried out under normal pressure. However, it is also possible to carry out the process under increased pressure or under reduced pressure (for example in a range from 0.5 to 5 bar).

The reaction with alkylsulphonic acid chlorides, starting from the corresponding free hydroxy compounds, is carried out in one of the abovementioned solvents and one of the bases, preferably with methylene chloride and triethylamine, in a temperature range from -20°C to +20°C, preferably 0°C, under normal pressure.

The azide radical is in general introduced by reaction of the corresponding alkylsulphonyloxy-substituted compounds with sodium azide in one of the abovementioned solvents, preferably dimethylformamide, in a temperature range from 50°C to +120°C, preferably 100°C, under normal pressure.

The ketones are prepared by known methods (Swern oxidation) starting from the corresponding hydroxy compounds.

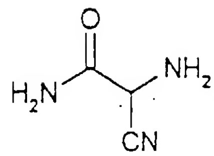
The enantiomerically pure compounds are accessible by customary methods, for example by chromatography of the racemic compounds of the general formula (I) on chiral phases.

The compounds of the general formula (III) are known.

The compounds of the general formula (IV) are new in most cases and can be prepared, for example, as described above.

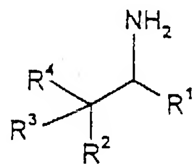
The compounds of the general formula (II) are new in most cases and can be prepared, for example, by a procedure in which

2-amino-2-cyanoacetamide of the formula (V)



(V)

is reacted with compounds of the general formula (VI)



(VI)

in which

R^1, R^2, R^3 and R^4 have the abovementioned meanings,

in inert solvents in the presence of triethyl orthoformate.

Suitable solvents for the individual steps of the processes are the customary organic solvents which do not change under the reaction conditions. These include, preferably, ethers, such as diethyl ether, dioxane, tetrahydrofuran or glycol dimethyl ether, or hydrocarbons, such as benzene, toluene, xylene, hexane, cyclohexane or petroleum fractions, or halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, dimethylformamide, hexamethylphosphoric acid triamide, acetonitrile, acetone or dimethoxyethane. It is also possible to use mixtures of the solvents mentioned. Acetonitrile is particularly preferred.

The process according to the invention is in general carried out in a temperature range from 0°C to +180°C, preferably from +30°C to +150°C.

These process steps according to the invention are in general carried out under normal pressure. However, it is also possible for them to be carried out under increased

pressure or under reduced pressure (for example in a range from 0.5 to 5 bar).

The compound of the formula (V) is known [cf. Logemann, G. Shaw, Chemistry and Industry, 1980 (13), 541-542].

The amines of the general formula (VI) are known in some cases or are new, and can then be prepared by known methods [cf. L.R. Krepski et al., Synthesis, 1986, 301-303].

The compounds of the general formula (I) according to the invention display an unforeseeable valuable pharmacological action spectrum.

They inhibit either one or more of the cGMP-metabolizing phosphodiesterases (PDE I, PDE II and PDE V). This leads to a differentiated increase in cGMP. An increase in the cGMP level can lead to an antithrombotic, vasodilatory and/or antiarrhythmic action. The selectivity is also determined by the distribution of the isoenzymes in the tissue.

The compounds according to the invention furthermore intensify the action of substances, such as, for example, EDRF (endothelium-derived relaxing factor) and ANP (atrial natriuretic peptide), which increase the cGMP level.

They can therefore be employed in medicaments for the treatment of inflammatory diseases, such as, for example, asthma, inflammatory dermatoses, for the treatment of high blood pressure, stable and unstable angina, peripheral and cardiac vascular diseases and of arrhythmias, for the treatment of thromboembolic diseases and ischaemias, such as myocardial infarction, cerebral stroke, transitory and ischaemic attacks, angina pectoris, peripheral circulatory disturbances, prevention of restenoses, such as after thrombolysis treatments, percutaneous transluminal angioplasties (PTA) and bypass, percutaneous transluminal coronary angioplasties (PTCA), bypass, septic shock and diseases of the urogenital system, such as, for example, prostate hypertrophy, impotence and incontinence.

A further aspect of the invention relates to the use of compounds of the invention in treatment of any of the above conditions, but especially an inflammation or a thromboembolic or cardiovascular disease or impotence in a mammal.

Another aspect of the invention relates to commercial packages comprising pharmaceutically effective amounts of compounds of the invention together with instructions for the above uses.

Activity of the phosphodiesterases (PDEs)

The cGMP-stimulatable PDE II, the cGMP-inhibitable PDE III and the cAMP-specific PDE IV were isolated from either porcine or bovine myocardium. The Ca-calmodulin-stimulatable PDE I was isolated from the porcine aorta or porcine brain. The cGMP-specific PDE V was obtained from the porcine small intestine, porcine aorta and/or human blood platelets. Purification was carried out by anion exchange chromatography over MonoQ^R Pharmacia essentially by the method of M. Hoey and Miles D. Houslay, Biochemical Pharmacology, Vol. 40, 193-202 (1990).

The enzyme activity is determined in a test batch of 100 µl in 20 mM Tris/HCl buffer of pH 7.5 which comprises 5 mM $MgCl_2$, 0.1 mg/ml of bovine serum albumin and either 800 Bq of ^{3}HcAMP or ^{3}HcGMP. The final concentration of the corresponding nucleotides is 10^{-6} mol/l. The reaction is started by addition of the enzyme and the amount of enzyme is chosen such that about 50% of the substrate is reacted during the incubation time of 30 minutes. To test the cGMP-stimulatable PDE II, ^{3}HcAMP is used as the substrate and 10^{-6} mol/l of non-labelled cGMP is added to the batch. To test the Ca-calmodulin-dependent PDE I, 1 µM $CaCl_2$ and 0.1 µM calmodulin are also added to the reaction batch. The reaction is stopped by addition of 100 µl of acetonitrile which comprises 1 mM cAMP and 1 mM AMP. 100 µl of the reaction batch are separated on the HPLC column and the cleavage products are determined quantitatively "online" with a flow-through scintillation counter. The substance concentration at which the rate of reaction is reduced by 50% is measured.

Inhibition of the phosphodiesterases in vitro

Example No.	PDE I IC_{50} [µM]	PDE II IC_{50} [µM]	PDE V IC_{50} [µM]
5	10	3	50
8	40	2	
14	4	0.6	0.3

Example No.	PDE I IC_{50} [µM]	PDE II IC_{50} [µM]	PDE V IC_{50} [µM]
20	1	0.4	1
25	3	0.1	10

The compounds were investigated for antihypertensive activity on anaesthetized pigs.

The antihypertensive activity was measured after intravenous administration to SHR rats.

To determine the cyclic nucleotides, heart and aorta tissue was removed and deep-frozen immediately. The samples were powdered under liquid N_2 and extracted with 70% ethanol and the content of cGMP and cAMP was determined with commercial radioimmunoassays (Amersham).

The erection-inducing action was measured on anaesthetized rabbits. (C.G. Stief et al. World Journal Urology 1990, pages 233-236).

The substances were administered in dosages of 0.1 to 10 mg/kg either directly into the corpus cavernosum or intraduodenally, rectally, orally, transdermally or intravenously.

The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, non-toxic, pharmaceutically suitable carriers or solvents. The therapeutically active compound should in each case be present here in a concentration of about 0.5 to 90% by weight of the total mixture, i.e. in amounts which are sufficient to achieve the stated dosage range.

The formulations are prepared, for example, by extending the active compounds with solvents and/or carriers, if appropriate using emulsifying agents and/or dispersing agents, it being possible, for example in the case of the use of water as a diluent, for

organic solvents to be used as auxiliary solvents if appropriate.

The formulations are administered in the customary manner, preferably orally, parenterally, transdermally, perlingually or intravenously.

In general, it has proved advantageous in the case of intravenous administration to administer amounts of about 0.01 to 10 mg/kg, preferably about 0.1 to 10 mg/kg, of body weight to achieve effective results.

Nevertheless, it may be necessary to deviate from the amounts mentioned, and in particular as a function of the body weight or the nature of the administration route, of the behaviour of the individual towards the medicament, of the nature of the formulation thereof and of the time or interval at which administration takes place. Thus, in some cases it may be sufficient to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the course of the day.

Starting compunds

General working instructions for the synthesis of the 1-substituted 5-acylamino-imidazole-4-carboxamides (formula IV)

Method A:

10 mmol of the 1-substituted 5-amino-imidazole-4-carboxamide and 15 mmol (60% strength dispersion in mineral oil) of NaH (or 30 mmol of NaH, if R^2 represents a hydroxyl group) are stirred in 50 ml of absolute tetrahydrofuran at 20°C for 3 hours (sparingly soluble imidazoles are refluxed for up to 3 hours). 10 mmol of acid chloride (or 20 mmol if a hydroxyl group is present) in 2.5 ml of absolute tetrahydrofuran are

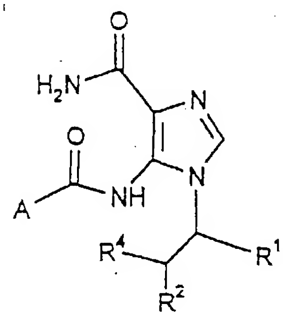
added dropwise at 20°C and the mixture is stirred overnight at room temperature. The solvent is removed on a rotary evaporator in vacuo, the residue is taken up in 50 ml of ethyl acetate and the mixture is shaken with 50 ml of water. The organic phase is separated off and dried with Na_2SO_4 and the solvent is evaporated in vacuo. The residue is purified by recrystallization or flash chromatography.

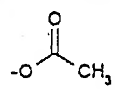
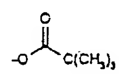
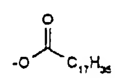
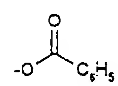
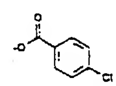
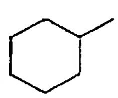
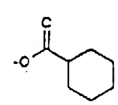
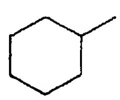
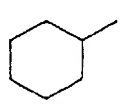
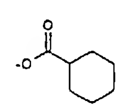
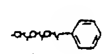
Method B:

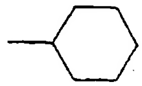
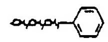
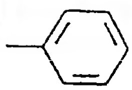
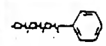
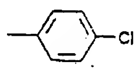
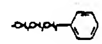
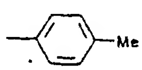
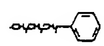
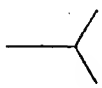
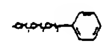
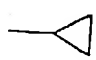
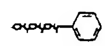
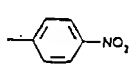
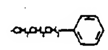
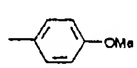
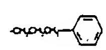
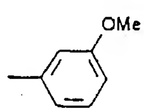
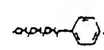
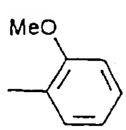
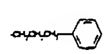
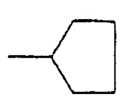
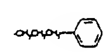
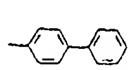
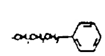
10 mmol of the 1-substituted 5-amino-imidazole-4-carboxamide are dissolved in 20 ml of dry pyridine. After addition of 50 mg of 4-dimethylaminopyridine (DMAP), 11 mmol of acid chloride (or 22 mmol, if R^2 represents a hydroxyl group) are added dropwise at 20°C (solid acid chlorides are dissolved in a little absolute toluene). The mixture is stirred at 20°C for 1 hour, and in some cases heating at 50°C for 1 - 2 hours is also necessary (monitoring by TLC). The batch is poured into 100 ml of ice-water and extracted by shaking 3 times with 50 ml of ethyl acetate each time. The combined ethyl acetate phases are washed twice with 1 N HCl and once with saturated NaCl solution, dried over Na_2SO_4 and evaporated in vacuo. The residue is purified by flash chromatography or recrystallization.

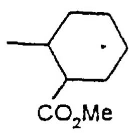
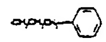
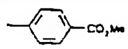
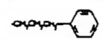
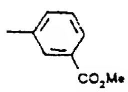
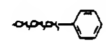
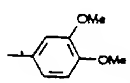
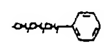
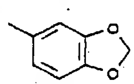
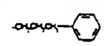
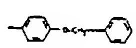
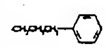
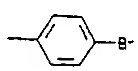
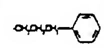
The 1-substituted 5-acylamino-imidazole-4-carboxamides listed in Table I are prepared by these two processes:

Table I:



Example No.	A	R^4	R^2	R^1	Method	Yield (% of theory)	R_f *)
I	$-CH_3$	CH_3		n-hexyl	A	33	0.40
II	$-C(CH_3)_3$	CH_3		n-hexyl	A	28	0.45
III	$-n-C_{17}H_{35}$	CH_3		n-hexyl	B	50	0.48
IV	$-C_6H_5$	CH_3		n-hexyl	A	19	0.39
V	$-4-Cl-C_6H_5$	CH_3		n-hexyl	A	15	0.40
VI		CH_3		n-hexyl	B	52	0.43
VII		CH_3	H	n-hexyl	A	16	0.38
VIII		CH_3			B	45	0.41

Example No.	A	R⁴	R²	R¹	Method	Yield (% of theory)	R_f *)
IX		H	H		B	41	
X		H	H		B	27.9	
XI		H	H		B	17.3	
XII		H	H		B	37.9	
XIII		H	H		B	29.2	
XIV		H	H		B	38.7	
XV		H	H		B	15.7	
XVI		H	H		B	18.3	
XVII		H	H		B	44.7	
XVIII		H	H		B		
XIX		H	H		B	48	
XX		H	H		B	34.8	

Example No.	A	R^4	R^2	R^1	Method	Yield (% of theory)	R_f *)
XXI		H	H		B	14.5	
XXII		H	H		B	11.4	
XXIII		H	H		B	28.7	
XXIV		H	H		B	11.7	
XXV		H	H		B		
XXVI		H	H		B		
XXVII		H	H		B	45	0.41

* Mobile phase: CH_2Cl_2 / MeOH 10:1

Preparation Examples

General working instructions for synthesis of the 2,9-disubstituted purin-6-ones (Formula I)

Method A:

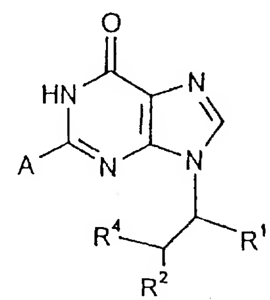
1 mmol of 1-substituted 5-acylamino-imidazole-4-carboxamide and 5 mmol of potassium carbonate are boiled under reflux overnight in 20 ml of ethanol and 10 ml of water. The solvent is evaporated in vacuo, the residue is taken up in 20 ml of ethyl acetate and the mixture is extracted by shaking with saturated NaCl solution. The organic phase is separated off, dried over Na_2SO_4 and evaporated in vacuo. The residue is purified by recrystallization or flash chromatography.

Method B: (analogous to EP 0526 004)

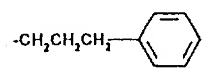
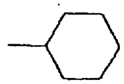
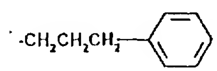
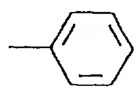
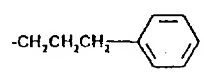
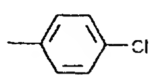
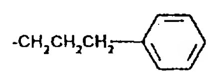
1 mmol of 1-substituted 5-acylamino-imidazole-4-carboxamide, 5 mmol of potassium carbonate and 1 ml of 30% H_2O_2 solution are boiled under reflux overnight in 10 ml of water and 10 ml of ethanol (monitoring by TLC). Further working up is carried out analogously to instructions A.

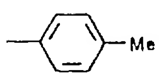
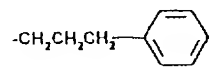
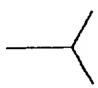
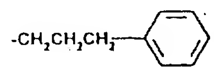
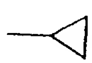
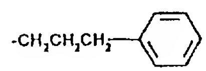
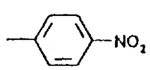
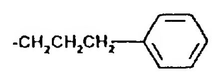
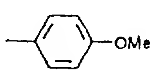
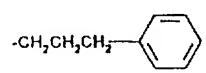
The 2,9-disubstituted purin-6-ones listed in Table 1 are prepared in accordance with these two instructions:

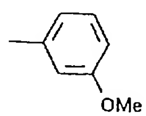
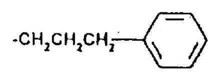
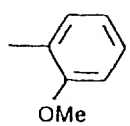
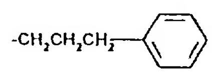
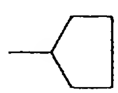
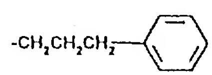
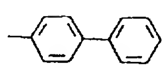
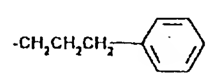
Table 1:

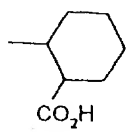
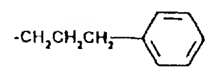
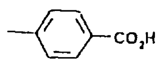
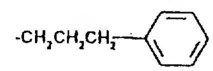
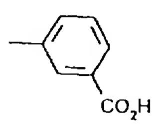
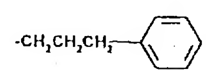
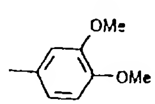
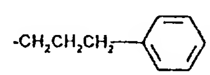


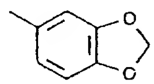
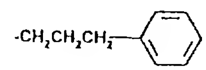
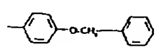
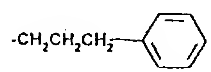
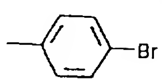
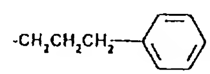
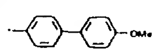
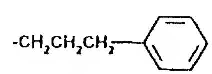
Example No.	A	R^4	R^2	R^1	Method	Yield (% of theory)	Melting point (°C) / R_f
1	$-CH_3$	CH_3	OH	n-hexyl	A	68.6	0.39 (CH_2Cl_2 / CH_3OH 10:1)
2	$-C(CH_3)_3$	CH_3	OH	n-hexyl	A	49.1	237 (ethyl acetate/diethyl ether)
3	$-n-C_{17}H_{35}$	CH_3	OH	n-hexyl	B	24.8	0.52 (CH_2Cl_2 / CH_3OH 10:1)
4	$-C_6H_5$	CH_3	OH	n-hexyl	A	48.9	249 (ethyl acetate/diethyl ether)
5	$-4-Cl-C_6H_4$	CH_3	OH	n-hexyl	A	27.9	235 (C_2H_5OH/ether)
6	$-C_6H_{11}$	CH_3	OH	n-hexyl	B	72.9	166 (ethyl acetate/diethyl ether)

Example No.	A	R^4	R^2	R^1	Method	Yield (% of theory)	Melting point (°C) / R_f
7	$-C_6H_{11}$	CH_3	H	n-hexyl	A	42.1	154 (ethyl acetate/diethyl ether)
8	$-C_6H_{11}$	CH_3	OH		B	43.5	0.44 (CH_2Cl_2 / CH_3OH 10:1)
9		H	H		A	44.9	162°C
10		H	H		A	40.3	212°C
11		H	H		A	34.2	184°C

Example No.	A	R^4	R^2	R^1	Method	Yield (% of theory)	Melting point (°C) / R_f
12		H	H		A	49.8	179°C
13		H	H		A	38.9	0.38
14		H	H		A	44.1	0.41
15		H	H		A	36	194°C
16		H	H		A	49.3	139°C

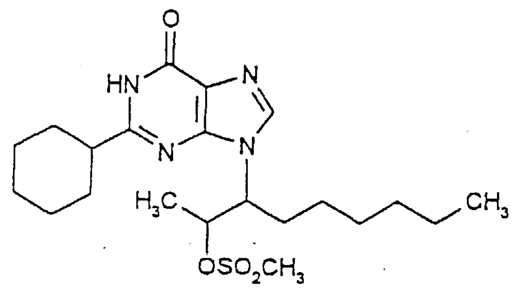
Example No.	A	R^4	R^2	R^1	Method	Yield (% of theory)	Melting point (°C) / R_f
17		H	H		A	41.7	125°C
18		H	H		A		
19		H	H		A	48.9	149°C
20		H	H		A	32.5	164°C

Example No.	A	R^4	R^2	R^1	Method	Yield (% of theory)	Melting point (°C) / R_f
21		H	H		A	35.1	128°C
22		H	H		A	29.2	235°C (decomposition)
23		H	H		A	44.6	243°C (decomposition)
24		H	H		A	37.1	195°C

Example No.	A	R^4	R^2	R^1	Method	Yield (% of theory)	Melting point (°C) / R_f
25		H	H		A	42.6	182°C
26		H	H		A	41.1	245°C
27		H	H		A	32.7	190°C
28		H	H		A	35	152°C

Example 29

9-(2-Methanesulphonyloxy-3-nonyl)-2-cyclohexyl-purin-6-one



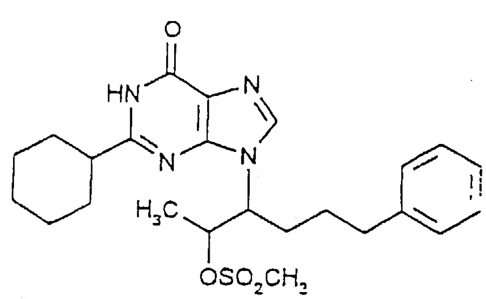
0.36 g (1 mmol) of 9-(2-hydroxy-3-nonyl)-2-cyclohexyl-purin-6-one (Example 6) and 0.3 ml of triethylamine are stirred in 5 ml of absolute CH_2Cl_2 at 0°C. 0.1 ml of methanesulphonyl chloride, dissolved in 2.5 ml of absolute CH_2Cl_2, is then added dropwise. After 30 minutes at 0°C, the mixture is extracted by shaking with 10 ml of saturated $NaHCO_3$ solution, 10 ml of 2 N HCl solution and 10 ml of saturated $NaHCO_3$ solution. The organic phase is dried over Na_2SO_4, the solvent is evaporated in vacuo and the residue is purified by flash chromatography using ethyl acetate/ CH_2Cl_2/CH_3OH 10:1 as the eluent.

Yield: 0.198 g (45.2%)

R_f = 0.52 (CH_2Cl_2 / CH_3OH 10:1)

Example 30

9-(2-Methanesulphonyl-6-phenyl-3-hexyl)-2-cyclohexyl-purin-6-one



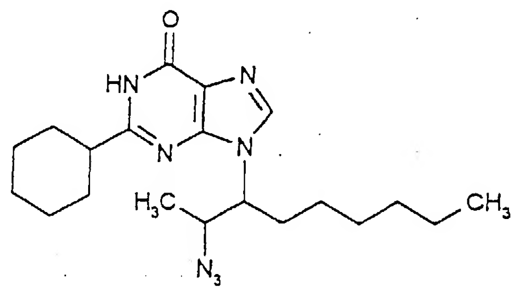
The title compound is prepared analogously to the instructions of Example 29 starting from 9-(2-hydroxy-6-phenyl-3-hexyl)-2-cyclohexyl-purin-6-one (Example 8).

Yield: 89.7%

R_f = 0.5 (CH_2Cl_2 / CH_3OH 10:1)

Example 31

9-(2-Azido-3-nonyl)-2-cyclohexyl-purin-6-one



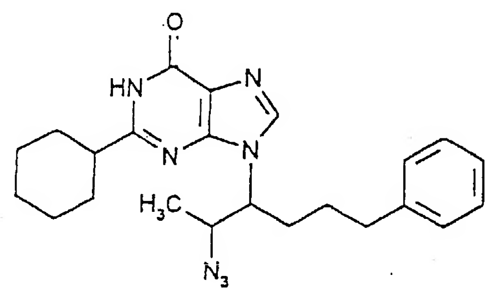
0.381 g (0.87 mmol) of 9-(2-methanesulphonyloxy-3-nonyl)-2-cyclohexyl-purin-6-one (Example 29) and 0.113 g (1.74 mmol) of sodium azide are stirred in 5 ml of absolute DMF at 100°C overnight. The mixture is cooled to 20°C, 30 ml of ethyl acetate are added and the mixture is washed twice with 50 ml of water each time and once with 50 ml of saturated NaCl solution. After drying over Na_2SO_4, the solvent is evaporated in vacuo and the residue is purified by flash chromatography (eluent: CH_2Cl_2 / CH_3OH 30:1).

R_f = 0.55 (CH_2Cl_2 / CH_3OH 10:1)

Yield: 0.311 g (92.8%)

Example 32

9-(2-Azido-6-phenyl-3-hexyl)-2-cyclohexyl-purin-6-one



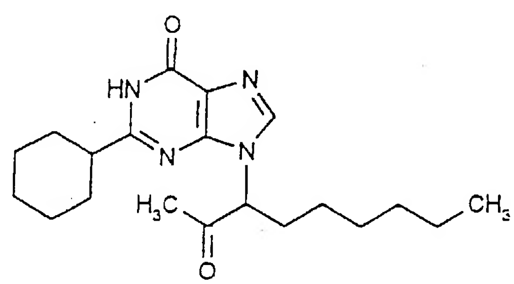
The title compound is prepared analogously to the instructions of Example 31 starting from 9-(2-methanesulphonyloxy-6-phenyl-3-hexyl)-2-cyclohexyl-purin-6-one (Example 30).

Yield: 0.372 g (78.2%)

R_f = 0.54 (CH_2Cl_2 / CH_3OH 10:1)

Example 33

9-(2-Oxo-3-nonyl)-2-cyclohexyl-purin-6-one



0.2 ml of absolute DMSO in 3 ml of absolute CH_2Cl_2 is added dropwise to 0.15 ml of oxalyl chloride in 5 ml of absolute CH_2Cl_2 at -60°C and the mixture is subsequently stirred at -60°C for 20 minutes. 540 mg (1.5 mmol) of 9-(2-hydroxy-3-nonyl)-2-cyclohexyl-purin-6-one (Example 6) in 3 ml of CH_2Cl_2 are then slowly added dropwise and the mixture is subsequently stirred at -60°C for 1 hour. 1 ml of triethylamine in 3 ml of CH_2Cl_2 is added dropwise to this solution. The mixture is allowed to come to

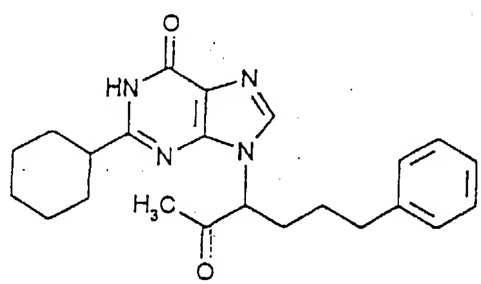
room temperature, 7 ml of water are added and the organic phase is separated off. The organic phase is washed with 10 ml of 2 N HCl and 10 ml of saturated NaCl solution, dried over Na_2SO_4 and evaporated in vacuo. The residue is purified by flash chromatography (eluent: CH_2Cl_2 / CH_3OH 40:1).

Yield: 0.416 g (77.4%)

R_f = 0.47 (CH_2Cl_2 / CH_3OH 10:1)

Example 34

9-(2-Oxo-6-phenyl-3-hexyl)-2-cyclohexyl-purin-6-one



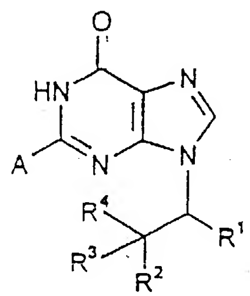
The title compound is prepared analogously to the instructions of Example 33 starting from 9-(2-hydroxy-6-phenyl-3-nonyl)-2-cyclohexyl-purin-6-one (Example 8).

R_f = 0.48 (CH_2Cl_2 / CH_3OH 10:1)

Yield: 48.8%

Patent Claims

1. 2,9-Disubstituted purin-6-one of the general formula (I)



(I),

in which

R^1 represents straight-chain or branched alkyl having 2 to 10 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by halogen, nitro, cyano or by straight-chain or branched alkyl having up to 6 carbon atoms,

R^2 represents hydrogen, hydroxyl or azido, or represents straight-chain or branched alkyl having up to 6 carbon atoms, or represents a group of the formula $-O-SO_2R^5$,

wherein

R^5 denotes straight-chain or branched alkyl having up to 4 carbon atoms or phenyl,

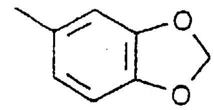
R^3 represents hydrogen,

or

R^2 and R^3 together form the radical of the formula =O,

R^4 represents hydrogen, or represents straight-chain or branched alkyl

having up to 4 carbon atoms, and

A represents a radical of the formula 

or represents straight-chain or branched alkyl having up to 20 carbon atoms, or represents cycloalkyl having 3 to 7 carbon atoms, or represents phenyl, each of which is optionally substituted up to 2 times in an identical or different manner by halogen, trifluoromethyl, carboxyl, nitro, cyano or by straight-chain or branched alkyl, alkoxycarbonyl or alkoxy having in each case up to 5 carbon atoms, which in their turn can be substituted by phenyl, or the rings are optionally substituted by phenyl, which in turn can be substituted by straight-chain or branched alkoxy having up to 5 carbon atoms,

or a pharmaceutically acceptable tautomer or salt thereof.

2. 2,9-Disubstituted purin-6-one of the formula according to Claim 1, in which

R^1 represents straight-chain or branched alkyl having 2 to 8 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by fluorine, chlorine, bromine, nitro, cyano or by straight-chain or branched alkyl having up to 4 carbon atoms,

R^2 represents hydrogen, hydroxyl or azido, or represents straight-chain or branched alkyl having up to 4 carbon atoms or a group of the formula $-O-SO_2R^5$,

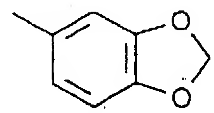
wherein

R^5 denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl,

R^3 represents hydrogen, or

R^2 and R^3 together form the radical of the formula =O,

R^4 represents hydrogen, or represents straight-chain or branched alkyl having up to 3 carbon atoms, and

A represents a radical of the formula 

or represents straight-chain or branched alkyl having up to 19 carbon atoms, or represents cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl, or represents phenyl, each of which is optionally substituted up to 2 times in an identical or different manner by fluorine, chlorine, bromine, nitro, carboxyl, hydroxyl or by straight-chain or branched alkyl, alkoxycarbonyl or alkoxy having in each case up to 4 carbon atoms, which in their turn can be substituted by phenyl, or the rings are optionally substituted by phenyl, which in turn is substituted by straight-chain or branched alkoxy having up to 4 carbon atoms,
or a pharmaceutically acceptable tautomer or salt thereof.

3. 2,9-Disubstituted purin-6-one of the formula according to Claim 1

in which

R^1 represents straight-chain or branched alkyl having 2 to 7 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by fluorine, chlorine, bromine, nitro, cyano or by straight-chain or branched alkyl having up to 3 carbon atoms,

R^2 represents hydrogen, hydroxyl or azido, or represents straight-chain or branched alkyl having up to 3 carbon atoms or a group of the formula

$-OSO_2R^5$,

wherein

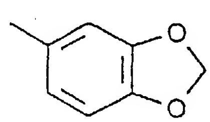
R^5 denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl,

R^3 represents hydrogen,

or

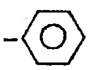
R^2 and R^3 together form the radical of the formula =O,

R^4 represents hydrogen, or represents straight-chain or branched alkyl having up to 3 carbon atoms, and

A represents a radical of the formula  or

represents straight-chain or branched alkyl having up to 18 carbon atoms, or represents cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl or represents phenyl, each of which is optionally substituted up to 2 times in an identical or different manner by fluorine, chlorine, bromine, hydroxyl, carboxyl, nitro or by straight-chain or branched alkyl, alkoxycarbonyl or alkoxy having in each case up to 3 carbon atoms, which in their turn can be substituted by phenyl, or the rings are optionally substituted by phenyl, which in turn can be substituted by straight-chain or branched alkoxy having up to 3 carbon atoms, or a pharmaceutically acceptable tautomer or salt thereof.

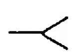
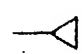
4. A compound according to claim 1, wherein

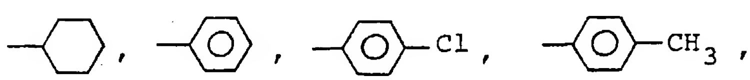
R^1 is n-hexyl or $-(CH_2)_3-$,

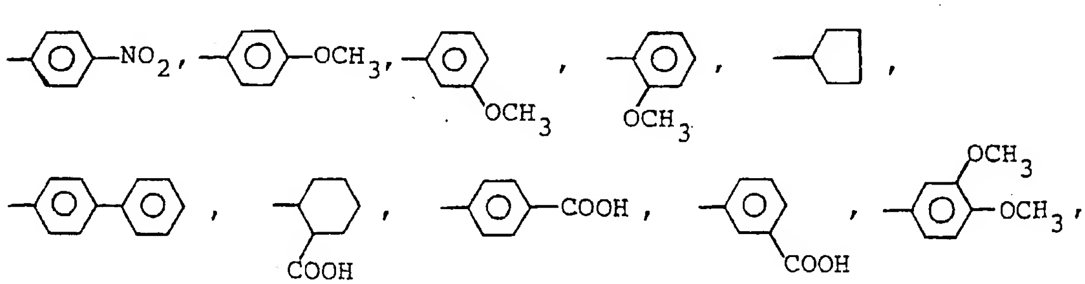
R^2 is hydrogen, hydroxyl, azido or $-OSO_2CH_3$,

R^2 and R^3 together are =O,

R^4 is H or CH_3, and

A is $-CH_3$, , $C(CH_3)_3$, $n-C_{17}H_{35}$, , C_6H_5,

$4-Cl-C_6H_4$, C_6H_{11}, 



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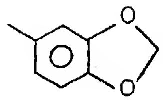
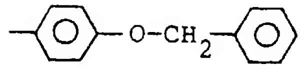
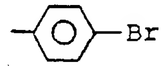
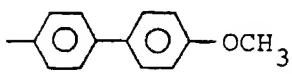
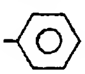
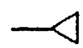
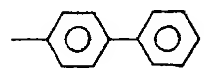
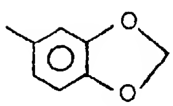
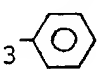
 ,  ,  or

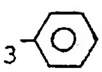
 .

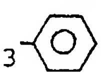
5. A compound according to claim 1, wherein
R^1 is n-hexyl or $-(CH_2)_3-$ ,
R^2 is hydrogen or hydroxyl,
R^4 is H or CH_3,
A is 4-Cl-C_6H_4, C_6H_{11},  ,  or

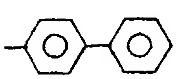
 .

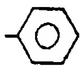
6. A compound according to claim 1, wherein R^1 is n-hexyl, R^2 is hydroxyl, R^4 is methyl and A is 4-chlorophenyl.

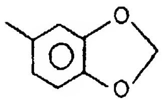
7. A compound according to claim 1, wherein R^1 is $-(CH_2)_3-$ , R^2 is hydroxyl, R^4 is methyl and A is cyclohexyl.

8. A compound according to claim 1, wherein R^1 is $-(CH_2)_3-$ , R^2 and R^4 each represent hydrogen and A is cyclopropyl.

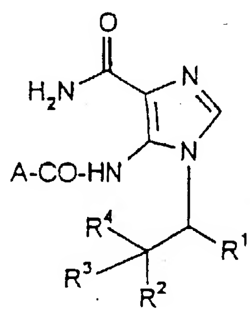
9. A compound according to claim 1, wherein R^1 is $-(CH_2)_3-$ , R^2 and R^4 each represent hydrogen and A is

 .

10. A compound according to claim 1, wherein R^1 is $-(CH_2)_3-$, R^2 and R^4 each represent hydrogen and A is


.

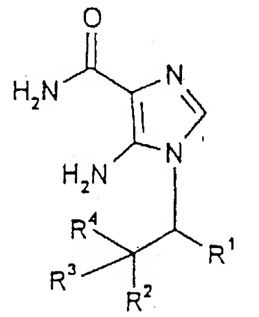
11. A process for preparing a compound of formula (I) according to any one of claims 1 to 10, which process comprises cyclizing a compound of formula (IV)



(IV)

in which A, R^1, R^2, R^3 and R^4 are as defined in any one of claims 1 to 10, in an inert solvent and in the presence of a base and, if required, introducing or derivatizing any of substituents R^1, R^2, R^3 and R^4 by acylation, oxidation or azide exchange.

12. Process for preparing a 2,9-disubstituted purin-6-one according to any one of claims 1 to 10, which process comprises a first step of reacting a compound of the general formula (II)

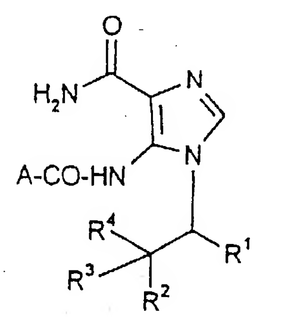


(II)

in which R^1, R^2, R^3 and R^4 are as defined in any one of claims 1 to 10, with a compound of the general formula (III)

A-CO-Cl (III)

in which A has the abovementioned meaning, in an inert solvent and in the presence of a base, to give a compound of the general formula (IV)



(IV)

in which A, R^1, R^2, R^3 and R^4 have the abovementioned meaning, and in a second step cyclizing said compound of formula (IV) in an inert solvent and in the presence of a base and, if required, introducing or derivatizing any of substituents R^1, R^2, R^3 and R^4 by acylation, oxidation or azide exchange.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10, as active ingredient in association with a pharmaceutically acceptable diluent or carrier.

14. A process for preparing a pharmaceutical composition according to claim 13, which process comprises bringing said active ingredient into association with said pharmaceutically acceptable diluent or carrier.

15. Use of a compound according to any one of claims 1 to 10, in treatment of an inflammation or a thromboembolic or a cardiovascular disease in a mammal.

16. A commercial package comprising a pharmaceutically effective amount of a compound according to any one of claims 1 to 10, together with instructions for use in treatment of an inflammation or a thromboembolic or a cardiovascular disease in a mammal.

17. Use of a compound according to any one of claims 1 to 10, in treatment of impotence in a mammal.

18. A commercial package comprising a pharmaceutically effective amount of a compound according to any one of claims 1 to 10, together with instructions for use in treatment of impotence in a mammal.

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